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Medical treatment beyond ACE inhibition: false promise or lack of vision?

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Undoubtedly angiotensin converting enzyme (ACE) inhibitors have had a major impact on the treatment of patients with chronic heart failure. They have conclusively been shown to improve symptoms and survival, and they may be capable of preventing the development of heart failure or delaying its progression. Intriguingly, they may also have direct effects on coronary artery atheroma. The CONSENSUS trial was the first to show an improvement in survival, but even in the group given enalapril mortality was still depressingly high.[1] The treatment arm of SOLVD confirmed the beneficial effect of ACE inhibitors on mortality but in patients with less severe disease.[2] Despite the undoubted improvement survival remains poor.

ACE inhibitors also increase maximal exercise tolerance, which is believed to be indicative of an improvement in symptoms. In none of the studies, however, did the patients' exercise capability return to normal, and in many it remained quite markedly reduced. How much these modest but significant improvements during maximal exercise tests in a laboratory are reflected in symptomatic improvement during normal daily life is unclear.

In asymptomatic patients with impaired left ventricular function the evidence that ACE inhibitors reduce the progression to overt heart failure is supportive. Although the total mortality in the prevention arm of the SOLVD trial was not affected by enalapril, composite end points that included death were reduced, as were rates of admission to hospital.[3] Evidence suggests that ACE inhibitors may reduce the development of heart failure after uncomplicated myocardial infarction and improve survival, but one study, CONSENSUS II, failed to show any benefit.[4 5]

So, although ACE inhibitors have favourable effects in heart failure, they are not the complete answer and we must continue to explore other treatments that might produce further benefit.

Diuretics and agents that cause natriuresis

Once patients have developed salt and water retention they will need treatment with an agent that causes sodium excretion. Traditionally diuretics, loop or thiazide, are used because they are potent and have a rapid onset of action. They improve symptoms in all grades of heart failure in addition to having beneficial effects on exercise capacity.[6] Although they are clearly effective, it has been suggested that there is no evidence from clinical trials that they improve survival[7]—neither of course is there for penicillin. Undoubtedly, diuretics improve survival in acute left ventricular failure and probably chronic heart failure. Despite their efficacy, however, diuretics have theoretical, if not practical, disadvantages. They activate neurohormonal mechanisms, particularly the renin-angiotensin system, as well as causing depletion of important electrolytes. They may also impair glucose tolerance, have detrimental effects on plasma lipid concentrations, and increase plasma urate concentrations.

Concern about neurohormonal stimulation has led to the investigation of agents that cause a natriuresis but which have no harmful neuroendocrine effects. These include the neutral endopeptidase inhibitors and orally active dopamine agonists. The endopeptidase inhibitors prevent the breakdown of atrial natriuretic peptide, resulting in increased circulating concentrations. As atrial natriuretic peptide has both vasodilator and natriuretic properties they have considerable theoretical attraction. Candoxatril, an orally active endopeptidase inhibitor, has been shown to have comparable natriuretic and diuretic effects to frusemide and, importantly, this is accompanied by suppression, not activation, of the renin-angiotensin system.[8 9] Beneficial effects on exercise capacity have been reported but long term studies are awaited.[10] Ibopamine, an orally active dopaminergic agent, also has natriuretic and diuretic effects and may not stimulate neurohormonal systems.[11] Both these agents, therefore, have potential advantages over diuretics and may prove to be useful alternatives or provide additional benefit when taken with ACE inhibitors.

Digoxin

Debate about the value of digoxin in patients with sinus rhythm continues. Several recent studies entailing the randomised withdrawal of digoxin have shown a deterioration in patients from whom digoxin was withdrawn.[12] These do not, however, prove benefit of digoxin when added to existing treatment. However, there is now reasonable but by no means conclusive evidence that digoxin is effective in patients with all grades of heart failure who have sinus rhythm and have been treated with diuretics. Studies have shown a reduction in rate of admission to hospital and the need for additional diuretics; a reduction in patients' symptoms and signs; and an increase in exercise tolerance and ejection fraction.[13–16]

Few studies have specifically assessed the efficacy of digoxin in conjunction with ACE

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inhibitors. One small study of 19 patients has examined the effects of digoxin, quinapril, and their combination in patients with mild heart failure (New York Heart Association class II).[17] The only additional benefit of digoxin was to cause an increase in left ventricular ejection fraction. Although most patients enrolled in the ACE inhibitor mortality trials were taking digoxin, it is not clear whether it was the combination of diuretics, digoxin, and ACE inhibitors or the ACE inhibitor alone that was responsible for the benefits seen. An additive effect is suggested by the results of a recent trial of withdrawing digoxin from patients with mild to moderate heart failure treated with diuretics and ACE inhibitors.[18] This showed a significant deterioration in quality of life, exercise tolerance, and ventricular function in patients who were given placebo. This study is, however, somewhat peculiar in that the dose of digoxin used (mean 0·38 mg/day) is well in excess of that usually given in clinical practice.

The effects of digoxin on mortality also remain unknown, but as it improves baroreceptor function and reduces sympathetic nervous system activation its effects may be beneficial. The answer to this should be provided by the ongoing DIG study, whose results are expected by 1995.

Direct acting vasodilators

Early studies of various vasodilator agents, particularly nitrates and hydralazine, showed beneficial haemodynamic effects, but whether this could lead to an improvement in long term prognosis was unclear. The first of the V-HeFT trials showed an improvement in mortality and symptoms with this combination whereas prazosin had no effect.[19] V-HeFT II showed that, although enalapril had a more favourable effect on mortality, the combination of hydralazine and isosorbide dinitrate improved exercise tolerance more.[20] This suggests that a rational approach to the treatment of heart failure would be the combination of an ACE inhibitor to improve survival and a more potent peripheral vasodilator to improve symptoms further. Giving isosorbide dinitrate to patients already taking captopril significantly improves central haemodynamics,[21] although in a larger study assessing bicycle exercise capacity no improvement was seen.[22]

The best evidence for an additional benefit of a direct acting vasodilator to an ACE inhibitor is with flosequinan. Two large multicentre studies showed an improvement in exercise tolerance and symptoms,[23 24] but further investigation of the effects of flosequinan has been stopped because of its adverse effect on survival. This may be because of its inotropic activity, which it has in addition to its vasodilatory properties. It is worth noting that the detrimental effect on survival was seen only at a high dose (100 mg) and not at a lower dose (75 mg), a similar result to that recently described with vesnarinone.[25]

Calcium antagonists

As ischaemic heart disease is the commonest cause of heart failure in the United Kingdom it is not surprising that there are many patients who have symptoms both of heart failure and angina. Calcium antagonists are powerful vasodilators with anti-ischaemic and, in some cases, antiarrhythmic properties. Unfortunately, despite short term haemodynamic improvement there is little evidence at present to support their long term use. Early studies with diltiazem, verapamil, and nifedipine showed these drugs to be deleterious in patients with chronic heart failure.[26–28] The reason for this probably relates to a combination of a negative inotropic effect and further neurohormonal activation. The new generation of calcium antagonists, including amlodipine and felodipine, have less negative inotropic effects and do not seem to stimulate neurohormonal systems.[29 30] Their effects on symptoms and exercise tolerance, however, remain inconsistent, with small uncontrolled studies of felodipine showing apparent benefit not seen in controlled studies.[30 31] One large multicentre trial has shown an improvement in exercise tolerance with amlodipine in patients already taking diuretics, digoxin, and captopril.[29]

The effects of these agents on mortality are currently under study.

Dopaminergic agents

Although parenteral dopaminergic compounds are extensively used in treating exacerbations of heart failure, experience with orally active agents is still limited. Ibopamine is the main agent currently in use as levodopa is associated with clinically significant side effects related to the central nervous system.[32] Ibopamine has vasodilator, inotropic, and natriuretic effects in addition to reducing plasma renin activity and noradrenaline concentrations.[33] Several studies have shown beneficial effects on exercise capacity and symptoms, although these data are inconclusive.[34 35] When compared with digoxin and ACE inhibitors it seems to have similar efficacy, but evidence of additional benefit in patients already receiving maximal conventional treatment is poor.[36 37] No information is yet available on mortality. Although the preliminary data are promising, additional controlled studies are clearly warranted.

Cyclic AMP phosphodiesterase inhibitors

The principal defect in heart failure is a loss of contractile function of the myocardium, so the possibility of improving contractility by drugs that have positive inotropic effects has obvious appeal. Cyclic adenosine monophophate (cAMP) phosphodiesterase inhibitors have combined inotropic and vasodilatory activity and theoretically should be of value in heart failure. Early uncontrolled studies with phosphodiesterase inhibitors produced conflicting evidence about the effects on exercise tolerance and quality of life.[38] Larger placebo controlled

Classification of effects of drugs other than ACE inhibitors on heart failure

Drug class	*Symptoms and quality of life*	*Exercise capacity*	*Mortality*
Diuretics	Beneficial	Beneficial	Possibly beneficial
Natriuretic agents	Beneficial	Beneficial	Unknown
Digoxin	Beneficial	Beneficial	Unknown
Direct vasodilators	Beneficial	Beneficial	Beneficial
Calcium antagonists	Beneficial	Possibly beneficial	Unknown
Dopaminergic drugs	Beneficial	Possibly beneficial	Unknown
Inotropes	Possibly beneficial	Possibly beneficial	Deleterious
β Blockers	Beneficial	Beneficial	Unknown

studies have also produced inconsistent data,[39 40] although there is evidence to suggest benefit when added to the treatment of patients who remain symptomatic despite treatment with ACE inhibitors and diuretics.[41]

Whatever benefit they may have on symptoms, the use of phosphodiesterase inhibitors is associated with an adverse effect on survival. Three large studies have confirmed worsening survival in patients treated with either milrinone or enoximone.[39 42 43] In the PROMISE study mortality at six months was increased by 28% in patients treated with milrinone.[42] In a study with enoximone in severely ill patients survival was reduced but quality of life was improved.[43]

In view of these studies it is unlikely that further cAMP phosphodiesterase inhibitors will be developed. However, this type of drug would probably be used only in patients with severe disease, and in these circumstances the patients may prefer an increase in quality of life and an improvement in symptomatic well-being at the possible expense of a reduced survival.

Vesnarinone is an inotropic agent of unknown mechanism of action. It has been shown to improve symptoms, and in one study it had a beneficial effect on survival at a low dose and a deleterious effect at higher doses.[25] This is similar to the effect of flosequinan. Quite what place it will have in the treatment of heart failure is unclear, particularly as at the low doses which have been shown to improve survival it does not produce haemodynamic changes.[44] Further studies on the effects of low doses on mortality and exercise capacity are probably required.

β Agonists and β blockers

The normal human heart contains both β_1 and β_2 adrenoreceptors, stimulation of which causes both inotropic and chronotropic effects. In patients with heart failure chronic adrenergic stimulation leads to a down-regulation of β_1 receptors and a relative increase in β_2 receptors.[45] Stimulation of these receptors by β agonists was thought to have beneficial effects because of increased inotropic activity. Despite acute haemodynamic improvement there is no evidence of long term efficacy, probably because of the development of tolerance due to further β receptor down-regulation. These agents also increase mortality.[46]

Xamoterol is a β_1 selective partial agonist that improves symptoms in patients with mild to moderate heart failure.[47] In patients with more severe heart failure, however, it also increases mortality.[48] This may be because it has predominant β antagonist activity in patients with high resting sympathetic tone, although excessive inotropic activity secondary to agonist activity has also been suggested.[49 50] The precise role for xamoterol in patients with heart failure has yet to be established, current recommendations being for use in mild heart failure only.

As it has become clear that complete and even partial β agonism is deleterious the emphasis has shifted to β antagonism in an attempt to attenuate the long term effects of long term sympathetic activation. Early studies of acute β blockade were inconsistent, although subsequent trials of greater duration have shown modest beneficial effects on the symptoms of heart failure and exercise capacity.[51] More recently β blockers that also cause peripheral vasodilatation have been developed and initial studies have provided encouraging results.[52 53] These benefits seem to be associated with a reduction in neurohormonal activity, particularly plasma noradrenaline concentration. In patients with idiopathic dilated cardiomyopathy treatment with metoprolol prevents clinical deterioration, improves symptoms and cardiac function, and was well tolerated over 12 months.[54] β Blockers may also benefit patients with heart failure secondary to ischaemic heart disease.[53 55] The effects of these drugs on survival has not yet been determined, but studies are in progress. The recent metoprolol trial failed to show any significant effect on mortality from all causes, though morbidity was improved.[54] Indirect evidence of a beneficial effect on mortality is provided by the post infarction trials, but clearly definitive studies are required.[56 57]

Antiarrhythmic agents

Both atrial and ventricular arrhythmias are common in patients with cardiac failure. Symptomatic arrhythmias should obviously be treated, but the management and clinical significance of asymptomatic arrhythmias are unclear. Sudden death, which is presumably due to an arrhythmia, is the mode of death in approximately half the patients. More than 80% of patients with moderate to severe heart failure have ectopic activity on Holter monitoring, half of them having non-sustained ventricular tachycardia. Ventricular tachyarrhythmias therefore occur in more than 40% of patients with heart failure and are said to be the commonest cause of sudden death.[58] Although the presence of these arrhythmias is an independent predictor of prognosis, it is not known whether specific antiarrhythmic treatment reduces mortality. Indeed, the use of antiarrhythmic agents in patients with reduced ventricular function increases mortality,[59] either because of a proarrhythmic effect of the drug or because most of the antiarrhythmic agents are negatively inotropic. Amiodarone, which is probably the least negatively inotropic agent, may be of

benefit, with several small studies showing improved survival and effective rhythm suppression.[60 61]

Treatment of the underlying failure and correction of electrolyte abnormalities may obviate the need for antiarrhythmic agents, and enalapril reduces the frequency of ventricular tachycardia.[62] This is perhaps a further mechanism by which ACE inhibitors reduce mortality. β Blockers have been reported to exert similar effects.[50]

Anticoagulants

In patients with atrial fibrillation and intracardiac thrombus warfarin is often prescribed, but there is little evidence to support its routine use in all patients with heart failure, particularly if they are in sinus rhythm. The incidence of thromboembolic disease in these patients is controversial, particularly after the recent publication of a retrospective analysis of the V-HeFT trial.[63] This suggested that the incidence of thromboembolism and stroke in patients with mild to moderate heart failure is not high and not significantly reduced with warfarin. There are few data on patients with more severe grades of heart failure, although a higher incidence of thromboembolic disease might be expected secondary to poor cardiac function and immobility. Anticoagulant treatment is not without risks. Careful control in patients in whom the severity of heart failure is changing is difficult so a prospective randomised trial of warfarin in all grades of heart failure (*w*arfarin *a*spirin *s*tudy of *h*eart failure; WASH) is currently under way in the United Kingdom.

Drugs in development

Clinical experience with some of the drugs previously described is clearly limited, but there are in addition a number of other drugs which are at an even earlier stage of development. These include renin and angiotensin II antagonists, prostacyclin analogues, free radical scavengers, and inodilators acting on sodium channels. Potentially of great benefit are the renin and angiotensin antagonists, particularly in view of the increasingly recognised role of the neurohormonal and adrenergic systems.[64] These agents seem to be effective in treating hypertension, but data on their effects in patients with heart failure are limited. In a recently reported short term study, blockade of the angiotensin II receptor with the antagonist losartan produced favourable haemodynamic effects in patients with symptomatic congestive cardiac failure.[65] These effects, however, were associated with neurohormonal activation, which may restrict its long term use.

Non-pharmacological methods

Although drugs are the mainstay of treatment in patients with cardiac failure, several studies have described various non-pharmacological techniques of potential benefit. In patients performing bicycle ergometry increasing the concentration of inspired oxygen improved exercise performance, but no benefit was seen in patients during the six minute walking test.[66 67] Exercise training alone may improve symptoms and aerobic capacity, with potentially beneficial effects on survival.[68] As these studies were restricted to patients with stable mild to moderate heart failure the effects on patients with more severe disease remain unknown. Recently, physiological dual chamber pacing has been shown to be a possible option in the management of heart failure, with two small studies reporting short and long term benefit in patients with dilated cardiomyopathy.[69 70]

Patients with end stage cardiac failure seem to benefit from haemofiltration, but until recently the effects in patients with mild to moderate symptoms were unknown. In 36 patients with mild to moderate heart failure (New York Heart Association class II–III), most of whom were taking an ACE inhibitor, a single session of haemofiltration improved symptoms and haemodynamics and reduced plasma noradrenaline concentration. These effects were noted four days after haemofiltration and interestingly were maintained for six months.[71]

Conclusion

ACE inhibitors have undoubtedly made a significant contribution to improving the quality and quantity of life of patients with heart failure. Clearly, however, their benefits are not enough. Currently, no single drug seems to affect significantly all the different aspects of the heart failure syndrome, and combinations of drugs, each with different actions, are likely to be more useful. Several studies in progress are assessing the effects of combined treatments. We need to define clearly what we are trying to achieve in treating patients; in those with severe symptoms the aim should be to improve well-being, and we may be prepared to do this at the expense of a possible reduction in survival. In those with mild symptoms, however, the major aim should be to increase survival and prevent progression of the disease. Different drugs will be needed to enable us to do this, but we must be careful not to discard drugs that are potentially useful in one situation because they are ineffective, or even harmful, in another.

The outlook for patients with heart failure has improved but in reality remains bleak. Additional treatments are still clearly needed and should be investigated rigorously. Preventing the development of heart failure may, however, assume greater importance than attempting to cure it.

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